

PATENT

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Applicant(s): Matthew During *et al.*
Application No: 09/863,179
Filing Date: May 23, 2001
Entitled: Glutamic Acid Decarboxylase
(GAD) Based Delivery Systems
Atty. Docket No: 102182-12
Confirmation No: 9640

Group Art Unit: 1632

Examiner: A.M. Falk

Certificate of Mailing (37 C.F.R. 1.8(a))

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Alexandria, VA 22313-1450

RULE 132 DECLARATION OF DR. MICHAEL KAPLITT

I, Michael G. Kaplitt, residing at 515 East 72nd Street, Apt. 34D, New York, New York, hereby declare as follows:

1. I received a Bachelor of Arts degree from Princeton University in Molecular Biology in 1987, a Tri-Institutional MD-PhD degree from the The Rockefeller University and Cornell University Medical College in 1993 and 1995. During my postdoctoral training at the Rockefeller University in the Laboratory of Biochemical Genetics and Metabolism, I was also an

intern in surgery and a resident in neurosurgery from 1995-1999. I was a Chief Resident in Neurosurgery at the New York Hospital–Cornell University Medical College from 1999-2000. I was also a Clinical Fellow in the Department of Stereotactic and Functional Neurosurgery at the University of Toronto from 2000-2001. I was appointed Director of the Laboratory of Molecular Neurosurgery, The New York Hospital-Cornell University Medical College and Fellow, The Rockefeller University from 1995-2000. I am currently Assistant Professor of Neurosurgery and Director, Laboratory of Molecular Neurosurgery, Weill Medical College of Cornell University, NY, NY; a Clinical Assistant Attending, Division of Neurosurgery, Dept. of Surgery, Memorial-Sloan Kettering Cancer Center, NY, NY; and an Adjunct Assistant Professor, Laboratory of Neurobiology and Behavior, The Rockefeller University, NY, NY. A copy of my Curriculum Vitae more fully explaining my qualifications, publications and appointments is attached as Exhibit A. I am an inventor on the above-referenced patent application.

2. I am familiar with the patent application at issue and, through this declaration, I present the evidence that was requested and discussed during the interview with Examiner Falk, at the United States Patent and Trademark Office, on October 24, 2003. In particular, evidence relating to the broader application of the invention to different neurological disorders or diseases.

3. The claimed invention relates to methods for altering expression of a glutamic acid decarboxylase (GAD) in a region of the brain . This is accomplished by identifying a target site in the central nervous system that requires modification and delivering a vector that comprises a nucleic acid sequence encoding glutamic acid decarboxylase (GAD) to target site of the central nervous system (e.g., a region of the brain), to alter expression of GAD in the region of the brain.

4. The invention also demonstrates the principal that expression of GAD in a region of the brain alleviates the symptoms of Parkinson's disease rodent and primate *in vivo* models for Parkinson's Disease.

5. One of the embodiments of the invention demonstrates that GAD transduction of neurons in the subthalamic nucleus (STN) increases inhibition in the substantia nigra (SN) and decreases the excitatory effect of STN stimulation on neurons in the SN. The results show that changing the excitatory projection from the STN to the SN into an inhibitory projection, using a

gene therapy approach, alleviates the symptoms of Parkinson's disease (*See* page 59, lines 16-20).

6. The same result was repeated in our extended study, the results of which are published by Luo *et al.* in Science "Subthlamic GAD Gene Therapy in a Parkinson's Disease Rat Model" (2003) 298: 425-429 (Exhibit B). This paper demonstrates that GAD gene transfer into glutamatergic excitatory neurons leads to an inhibitory bias with altered network activity. This phenotypic shift provides strong neuroprotection and demonstrates there is plasticity between excitatory and inhibitory neurotransmission in the mammalian brain that results in a therapeutic effect.

7. The same inventive concept of delivering GAD to a region of the central nervous system, can be applied to any CNS disease in which increasing GABA production is desirable.

8. As further evidence that the invention can be applied to different diseases -- as well as different regions of the CNS -- a post-graduate student working at Neurologix, Inc., (licensee of the present invention) carried out the same method disclosed in the instant application in an animal model of epilepsy. This work, described below, shows that the symptoms of epilepsy can be reduced by delivering GAD to a region of the brain involved in epilepsy, e.g., the hippocampus.

9. The epilepsy experiment involved delivering three AAV vectors, AAV/CBA-hGAD65-1.76-WPRE-BGH ("GAD65"); AAV/CBA-hGAD67-WPRE-BGH ("GAD65"); and AAV-EGFP ("EGFP"), into three experimental groups of animals. A fourth sham group ("SHAM") of animals, was subject to injection with an empty needle as a control for injury related to insertion of a needle into the brain tissue. Two microliters of each of the AAV vector, at a genomic titer of 2×10^{10} genomes/ml, was infused bilaterally into the rat hippocampus using stereotaxic surgery.

10. Four weeks after vector administration, 10mg/kg kainic acid (i.p.) was administered to each animal to induce seizures. The animals were observed for the next 90 minutes for a variety of behavioural characteristics and by electroencephalograms of seizure activity. Figure 1 (Exhibit C) shows the results from an electroencephalogram of seizure activity

in the hippocampus of a rat kainic acid model for epilepsy. The data shows that rats treated with GAD, in particular, GAD65, have reduced seizures compared with the rats treated with EGFP or the SHAM group that received no vector. The results show that expression of GAD in a region of the brain associated with epilepsy provides neuroprotection against seizures.

11. Further evidence that GAD can be delivered to a selected region of the CNS is presented in Boulis *et al.*, “Stereotactic Gene Based Hypothalamic Neuromodulation” (2002) AANS meeting, Chicago (abstract) (Exhibit D).

12. In Boulis *et al.* an AAV-GAD construct, disclosed in the instant application, was used to deliver GAD to the lateral nucleus of the hypothalamus of rats to augment GABA production in the region. The delivery of GAD resulted in altered gene expression and sustained enhancement of GABA production in a deep brain target, which resulted in an alteration of metabolic behavior.

13. Another example of how GAD can be delivered to selected regions of the brain is shown in Jasmin *et al.* in Nature, “Analgesia and hyperalgesia from GABA-mediated modulation of the cerebral cortex” (2003) 424:316-320. (Exhibit E).

14. In Jasmin *et al.*, GABA neurotransmission in the rostral agranular insular cortex (RAIC) of freely moving rats, was altered by locally increasing GABA using two methods: (a) an enzyme inhibitor; and (b) a double-cassette-defective Herpes Simplex Virus (HSV) vector. Use of gene transfer mediated by a viral vector produced lasting analgesia in the rats by enhancing the descending inhibition of spinal nociceptive neurons. This reference further evidences that a variety of vectors may be used to deliver GAD in a targeted manner and alter GABA levels in relevant regions of the CNS.

15. A further example showing that delivering GAD to a region of the central nervous system, may be applied to any relevant disease is evidenced by a recent article by Levanthal *et al.* in Science “GABA and Its Agonists Improve Visual Cortical Function in Senescent Monkeys” (2003) 300:812-815 (Exhibit F).


16. Leventhal *et al.* demonstrated that the alteration of GABA levels, in a region of the visual cortex (V_1) of aged primates resulted in improved acuity -- including improved orientation and direction selectivity, decreased spontaneous activity and an increased ability to signal visual stimuli. This is further evidence that methods of altering GABA levels, such as delivering GAD to the central nervous system, can be used to address a variety of neurodegenerative diseases.

17. Thus one of ordinary skill in the art, would be able to use the application's disclosure, in addition to the knowledge available in the art, to apply the invention to alter expression of glutamic acid decarboxylase (GAD) in a selected region of the brain.

18. In summary, the disclosure in the application, in combination with the knowledge available in the art, would enable one skilled in the art to perform the full scope of the claimed invention without undue experimentation.

19. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 10001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 11/6/03


Michael G. Kaplitt, M.D., Ph.D.

Curriculum Vitae

Michael G. Kaplitt, MD PhD

Dept. of Neurosurgery, Weill Medical College of Cornell University

525 E.68th St., New York, N.Y. 10021

Phone: 212-746-5265

Fax: 212-746-8226

e-mail: mik2002@med.cornell.edu

PRESENT POSITIONS

Assistant Professor of Neurosurgery and Director, Laboratory of Molecular Neurosurgery, Weill Medical College of Cornell University, NY, NY

Clinical Assistant Attending, Division of Neurosurgery, Dept. of Surgery, Memorial-Sloan Kettering Cancer Center, NY, NY

Adjunct Assistant Professor, Laboratory of Neurobiology and Behavior, The Rockefeller University, NY, NY

PROFESSIONAL EXPERIENCE

Clinical Fellow, Stereotactic and Functional Neurosurgery, 2000-2001
Univ. of Toronto (Western Division), Toronto, Ontario, Canada

Chief Resident in Neurosurgery 1999-2000

Resident in Neurosurgery 1996-1999

Intern in Surgery, 1995-1996

The New York Hospital-Cornell University Medical College

Post-Doctoral Fellow 1995-1999

Laboratory of Biochemical Genetics and Metabolism, The Rockefeller University

EDUCATION

Tri-Institutional MD-PhD Program

Cornell University Medical College 1993-1995 MD

The Rockefeller University 1989-1993 PhD (Molecular Neurobiology)

University of Rochester
School of Medicine (MD-PhD program) 1987-1989

Princeton University 1983-1987 AB (Molecular Biology)
Cert. of Proficiency in Russian Studies

MEDICAL LICENSURE/BOARD CERTIFICATION

Licensed in NY. Board eligible, American Board of Neurological Surgery.

PERSONAL INFORMATION

Birthplace: Brooklyn, N.Y. Birthdate: September 1, 1965

Marital Status: Separated, Children: 1 Son (Jeremy David Kaplitt)

HONORS, AWARDS AND FELLOWSHIPS

Magna Cum Laude, Princeton University

Certificate of Proficiency in Russian Studies, Princeton University

Varsity Letter, Men's Swimming, Princeton University

Founding Editor-in-Chief, Journal of the Univ. of Rochester Medical Center

National Research Service Award Graduate Fellowship

1992 Albert Cass Traveling Fellowship

1994 Saul R. Korey Award for Experimental Neurology, American Academy of Neurology

Sigma Xi Scientific Honor Society

1998 Distinguished Housestaff Award, The New York Hospital-Cornell Medical Center

2000 Fellowship Award, Medical Research Council of Canada

Second place poster, 2001 Congress of Neurological Surgeons

2002 Charles Elsberg Fellowship in Neurological Surgery, New York Academy of Medicine

2002 New Scholar in Aging Research, Ellison Foundation for Medical Research

PROFESSIONAL ACTIVITIES

Member, Neural Disorders Committee, American Society for Gene Therapy

Course Director, Update in Movement Disorder Surgery CME Course, Weill Medical College of Cornell University

Journal Editorial Board Member, Surgical Neurology

Section Editor for Stereotactic and Functional Neurosurgery, Select Reviews in Neurosurgery

Editor, World Society for Stereotactic and Functional Neurosurgery Website

Program Committee, 2001 Quadrennial Meeting, World Society for Stereotactic and Functional Neurosurgery

Program Committee, 2003 Quadrennial Meeting, American Society for Stereotactic and Functional Neurosurgery

Ad Hoc Reviewer, National Cancer Institute

Ad Hoc Reviewer, National Institutes of Neurological Disorders and Stroke

Admissions Committee Member, Weill Medical College of Cornell University

RESEARCH EXPERIENCE

2001-Present Director, Laboratory of Molecular Neurosurgery, Weill Medical College of Cornell University; Adjunct Faculty, The Rockefeller University

Examining effects of deep brain stimulation upon changes in gene expression in brain and mechanisms of such regulation

Developing new method for use of deep brain stimulation to treat chronic drug addiction

Identified new elements which regulate a novel form of circular replication of adeno-associated virus (AAV); further defining mechanisms and consequences of replication and packaging of these circular forms

Studying the effects of anti-oncogene expression on neuronal function and sensitivity to neurodegenerative disorders

Further developing the first clinical protocol for gene therapy for Parkinson's disease to initiate a Phase I clinical trial

2000-2001 Fellow, Stereotactic and Functional Neurosurgery, The University of Toronto, and Adjunct Faculty, The Rockefeller University

Used chronic *in vivo* microdialysis to analyze neurochemical changes in the subthalamic nucleus and substantia nigra of patients undergoing subthalamic nucleus deep brain stimulation for Parkinson's disease

Began exploration of gene expression changes in response to deep brain electrical stimulation in rodent models

1995-2000 Director, Laboratory of Molecular Neurosurgery, The New York Hospital-Cornell University Medical College and Fellow, The Rockefeller University

°Applications of viral vectors for study and of genes associated with Alzheimer's disease and exploration of potential gene therapy approaches

°Development of novel viral vectors and packaging systems for improved and safer CNS gene delivery.

°Application of viral vectors to study and treatment of Parkinson's disease, epilepsy, Alzheimer's disease and brain tumors.

°Demonstrated the first expression of a foreign gene in mammalian heart using an adeno-associated viral vector.

°Exploration of influence of estrogen upon brain function and disorders including Alzheimer's disease, ischemia and trauma

°Discovered that steroid receptors can act as enzymes to promote proper folding of certain proteins.

1993-1995 Post-doctoral fellow, Laboratory of Neurobiology and Behavior, The Rockefeller University and Department of Neurosurgery, Yale University School of Medicine.

°Applications of novel vectors to treatment of mammalian diseases, with particular emphasis upon adeno-associated viral vectors and adenoviral vectors.

°Demonstrated the first expression of a foreign gene in mammalian brain using an adeno-associated viral vector.

°Developed genetic therapy approach for Parkinson's disease, with therapeutic improvement in a rodent model. Primate studies were initiated with promising results.

°Applications of these vector systems to neuro-oncology were explored, with emphasis upon study of anti-oncogenes and genes associated with paraneoplastic syndromes.

1989-1993 Doctoral Research, Lab. of Neurobiology and Behavior, The Rockefeller Univ.

°Use of herpes simplex virus (HSV) defective viral vectors as agents for transfer of foreign gene into the adult mammalian brain *in vivo*.

°Demonstrated the first expression of a foreign gene in rat brain using a defective HSV vector.

°Applied the vector system as a novel approach to study gene regulation, and identified important elements of the rat preproenkephalin promoter using this system.

°Demonstrated that expression of the neuronal protein GAP-43 can induce formation of processes resembling neurites.

°Use of mutant HSV strains as possible therapeutic agents for the treatment of CNS neoplasms.

1987-1989 Laboratory of Drs. Thomas Broker and Louise Chow, University of Rochester.

°Analysis of the DNA binding domain of the human papillomavirus E2C protein, and attempted to develop non-radioactive *in situ* hybridization techniques for use in analysis of cervical cancer specimens.

1985-1987 Laboratory of Dr. Thomas Shenk, Princeton University. °Analysis of the basis for tumorigenicity of adenovirus type 9, a unique strain which specifically causes mammary fibroadenomas only in sexually intact female rats.

Summer, 1985 Molecular Diseases Branch, National Heart, Lung and Blood Institute

° Assisted in the cloning and sequencing of the human apolipoprotein B-100 gene.

Major Invited Lectures (Not including meeting abstracts/presentations from submissions)

Athena Neuroscience Corp., South San Francisco, CA (1992, 1994)

Rudolph Magnus Institute, University of Utrecht, The Netherlands (1992, 1993)

Schering-Plough Pharmaceuticals Corp., NJ (1992)

Tel-Aviv University, Tel Aviv, Israel (1992, 1994)

Weizmann Institute for Science, Rehovot Israel (1992)

Burke Rehabilitation Center, White Plains, NY (1994)

Cornell Medical College, Dept. of Neurology Grand Rounds, New York, NY (1994, 1998, 2001)

Harvard Medical School, Neurogenetics Unit, Boston, MA (1994)

Netherlands Institute for Brain Research, Amsterdam, The Netherlands (1994)

International Conference on Gene Therapy for CNS Disorders, Philadelphia, PA (1995)

Workshop on Basal Ganglia Disorders, UCLA School of Med., Los Angeles, CA (1995)

Rockefeller University, Clinical Research Seminar Series, New York, NY (1995)

Washington University School of Medicine, St. Louis, MO (1995)

International Congress on Endovascular Interventions X, Phoenix, AZ (1996)

Society for Neuroscience Symposium on Gene Transfer (Sponsored by NIMH, NIH) (1996)

NIH, NINDS, Laboratory of Molecular Disorders and Neuroscience, Bethesda, MD (1997)

Albert Einstein College of Medicine, Dept. of Radiation Oncology, Bronx, NY (1999)

Methodist Hospital, Conference on Movement Disorders, Brooklyn, NY (2000)

New York State Neurosurgical Society, Lake George, NY (2000)

2000 Botterell Symposium, University of Toronto, Toronto, Canada (2000)

Grand Rounds, Dept. of Surgery, Memorial-Sloan Kettering Cancer Center, NY, NY (2001)

International Conference on Aging 2001, Mt. Sinai School of Medicine, NY, NY (2001)

Contemporary Management of Movement Disorders, Practical Clinic, AANS (2001)

Contemporary Management of Movement Disorders, Practical Clinic, CNS (2001)

International Conference on Monitoring Molecules in Neuroscience, Dublin, Ireland (2001)

Contemporary Management of Movement Disorders, Practical Clinic, AANS (2002)

Contemporary Management of Movement Disorders, Practical Clinic, CNS (2002)

Plenary lecture, 5th Annual American Society for Gene Therapy Annual Meeting (2002)

University of Rochester Neurosurgery Grand Rounds and Neuroscience Seminar (2002)

Pain Service Seminar Series, Memorial Sloan-Kettering Cancer Center (2003)

Cornell-Salzburg Medical Seminar in Neurosurgery, Faculty (2003)

Program in Biomedical Science Seminar Series, Boston Univ. School of Medicine (2003)

Gene Therapy: The Next 5 Years, American Society for Microbiology (2003)

Contemporary Management of Movement Disorders, Practical Clinic, CNS (2002)

6th Annual American Society for Gene Therapy Annual Meeting (2003)

Update in Neuro-Oncology, Weill Medical College of Cornell University (2003)

BIBLIOGRAPHY

Books and Book Chapters

1. **Kaplitt MG** and Loewy AD, **Editors.** (1995) Viral Vectors: Gene Therapy and Neuroscience Applications. San Diego, CA: Academic Press.
2. Mobbs CV, **Kaplitt MG** and Pfaff DW (1997) "HIP-70/GRP58/Erp61/PLC-a/CPT: A single gene product and member of the protein disulfide isomerase gene family with thiol oxidoreductase activity subject to neuroendocrine regulation", in Prolyl Hydroxylase, Protein Disulfide Isomerase and Other Structurally Related Proteins (Guzman N, ed.) New York: Marcel Dekker, Inc.
3. **Kaplitt MG** and Loewy AD (1998) "Viral Vectors", in Fundamental Neuroscience (Bloom, et. al. eds) San Diego, CA: Academic Press.
4. **Kaplitt MG** and Lozano, AM (2001) Surgical drug delivery for neurodegenerative diseases. *Clin Neurosurg* 48:127-144.
5. **Kaplitt MG**, Hutchinson W and Lozano, AM (2001) "Target Localization in Movement Disorder Surgery", in Contemporary Clinical Neurology: Surgical Treatment of Parkinson's Disease and Other Movement Disorders (Tarsy, D. et. al., eds.) Totowa, NJ: Humana Press.
6. **Kaplitt MG**, Dostrovsky J, Hutchinson W and Lozano AM "Microelectrode Recording in Functional Neurosurgery" in Neurosurgery (Wilkins, RH and Rengachary, SS, eds.). New York: McGraw-Hill. In press.
7. **Kaplitt MG** and Loewy AD (2002) "Viral Vectors", in Fundamental Neuroscience, 2nd ed. (Bloom, et. al. eds) San Diego, CA: Academic Press.
8. Kaplitt MG, Rezai AR, Lozano A and Tasker R "Deep Brain Stimulation for Chronic Pain" in *Youmans Neurological Surgery, 5th Edition* (H.R. Winn, ed.). Philadelphia: Elsevier, In press.
9. **Kaplitt MG** and During MJ, **Editors.** Gene Transfer in the Brain: From Basic Science to Human Therapy. San Diego, CA: Academic Press. In preparation.

Publications

1. Mobbs CV, **Kaplitt MG**, Kow L-M, Pfaff DW (1991) PLC-a: A common mediator of the action of estrogen and other hormones? *Mol. Cell. Endocrinol.* 80:C187-C191.
2. **Kaplitt MG**, Pfaus JG, Kleopoulos SP, Hanlon BA, Rabkin SD, Pfaff DW (1991) Expression of a functional foreign gene in adult mammalian brain following in vivo transfer via a herpes simplex virus type 1 defective viral vector. *Mol. Cell. Neurosci.* 2:320-330.

3. **Kaplitt MG**, Rabkin SD, Pfaff DW (1992) Molecular alterations in nerve cells: Direct manipulation and physiologic mediation. *Curr. Top. Neuroendocrinol.* **11**:169-191.
4. **Kaplitt MG**, Kleopoulos SP, Pfaff DW, Mobbs CV. (1993) Estrogen induces HIP-70/PLC- α messenger RNA in the uterus and ventromedial hypothalamus. *Endocrinology* **133**:99-104.
5. Brooks PJ, **Kaplitt MG**, Kleopoulos SP, Funabashi T, Mobbs CV, Pfaff DW. (1993) Sensitive detection of low abundance RNAs by in situ hybridization using single-stranded DNA probes produced by amplified primer extension labeling. *J. Histochem. Cytochem.* **41**:1761-1766.
6. **Kaplitt MG**, Kwong AD, Kleopoulos SP, Mobbs CV, Rabkin SD, Pfaff DW. (1994) Preproenkephalin promoter yields region-specific and long-term expression in adult rat brain following in vivo transfer via a defective herpes simplex viral vector. *Proc. Natl. Acad. Sci. USA*, **91**:8979-8983.
7. **Kaplitt MG**, Leone P, Samulski RJ, Xiao X, Pfaff DW, OMalley K, During MJ (1994) Long-term expression and phenotypic correction using adeno-associated virus vectors in the mammalian brain. *Nature Gen.* **8**:148-154.
8. **Kaplitt MG**, Tjuvajev J, Leib DA, Berk J, Rabkin SD, Posner JB, Pfaff DW, Blasberg RG. (1994) Mutant herpes simplex virus induced regression of tumors growing in immunocompetent rats. *J. Neuro-oncology* **19**:137-142.
9. Verhaagen J, Hermens W, Oestricher B, Rabkin SD, Pfaff DW, Gispen WH, **Kaplitt MG** (1994) Expression of B-50 (GAP43) via a defective herpes simplex virus vector yields morphological changes in cultured non-neuronal cells. *Mol. Brain Res.* **26**:26-36
10. Dutt A, **Kaplitt MG**, Kow LM, Pfaff DW. (1994) Prolactin, CNS and Behavior, a critical review. *Neuroendocrinol.* **59**:413-419.
11. Yin J, **Kaplitt MG**, Pfaff DW (1994) In situ PCR and in vivo detection of foreign gene expression in rat brain. *Cell Vision* **1**:58-59.
12. Eizenberg O, **Kaplitt MG**, Eitan S, Pfaff DW, Hirschberg DL, Schwartz M. (1994) Linear dimeric interleukin-2 obtained by the use of a defective viral vector: conformation-activity relationship. *Mol. Brain Res.* **26**:156-162.
13. Wood MJA, Byrnes A, **Kaplitt MG**, Pfaff DW, Rabkin SD, Charlton HD (1994) Specific pattern of defective HSV1 gene transfer in the adult central nervous system: Implications for gene targeting. *Exp. Neurol.* **130**:127-140.
14. Rosenfeld MR, Meneses PM, Dalmau J, Drobnjak M, Cordon-Cardo C, **Kaplitt MG** (1995) Gene transfer of wild-type p53 results in restoration of tumor-suppressor function in a medulloblastoma cell line. *Neurology* **45**:1533-1539.

15. Tjuvajev J, Gansbacher B, Desai R, Beattie B, **Kaplitt MG**, Matei C, Koutcher J, Gilboa E, Blasberg R. (1995) RG-2 glioma growth attenuation and severe brain edema caused by local production of interleukin-2 and interferon-gamma. *Cancer Res.* **55**:1902-1910.
16. Holtmaat AJ, Hermens WT, Oestreicher AB, Gispen WH, **Kaplitt MG**, Verhaagen J. (1996) Efficient adenoviral vector directed expression of a foreign gene to neurons and sustentacular cells in the mouse olfactory neuroepithelium. *Mol. Brain Res.* **41**:148-156.
17. **Kaplitt M**, Gouras GK, Makimura H, Jovanovic J, Sweeney D, Greengard P, Relkin NR, Gandy S. (1996) Apolipoprotein E, A beta-amyloid, and the molecular pathology of Alzheimer's disease. Therapeutic implications. *Ann. N.Y. Acad. Sci.* **802**: 42-9.
18. **Kaplitt MG**, Xiao X, Samulski RJ, Li R, Ojamaa K, Klein IL, Makimura H, Kaplitt MJ, Strumpf RK, Diethrich EB (1996) Long-term gene transfer in porcine myocardium after coronary infusion of an adeno-associated virus vector. *Ann. Thoracic Surg.* **62**(6): 1669-76.
19. Vogt L, Giger RJ, Ziegler U, Kunz B, Buchstaller A, Hermens W, **Kaplitt MG**, Rosenfeld MR, Pfaff DW, Verhagen J, Sonderegger P (1996) Continuous renewal of the axonal pathway sensor apparatus by insertion of new sensor molecules into the growth cone membrane. *Current Biology* **6**(9): 1153-8.
20. Freese A, Stern M, **Kaplitt MG**, O'Connor WM, Abbey MV, O'Connor MJ, During MJ (1996) Prospects for gene therapy in Parkinson's disease. *Movement Disorders* **11**:469-488.
21. Freese A, During MJ, Davidson BJ, Gennarelli TA, **Kaplitt MG**, Flamm ES, Snyder PJ (1996) Transfection of human lactotroph adenoma cells with an adenovirus vector expressing tyrosine hydroxylase decreases prolactin release. *J. Clin. Endocrinol. Metab.* **81**: 2401-4.
22. Freese A, **Kaplitt MG**, WM OC, Abbey M, Langer D, Leone P, MJ OC, During MJ (1997) Direct gene transfer into human epileptogenic hippocampal tissue with an adeno-associated virus vector: implications for a gene therapy approach to epilepsy. *Epilepsia* **38**:759-66.
23. Holtmaat AW, Hermens V, Sonnemans MAF, Giger RJ, Van Leeuwen FW, **Kaplitt MG**, Oestreicher AB, Gispen WH, Verhaagen J (1997) Adenoviral Vector-Mediated Expression of B-50/GAP-43 Induces Alterations in the Membrane Organization of Olfactory Axon Terminals In Vivo. *J Neurosci* **17**:6575-86.
24. **Kaplitt MG**, Makimura H (1997) Defective viral vectors as agents for gene transfer in the nervous system. *J Neurosci Methods* **71**:125-32.
25. O'Connor WM, Davidson BL, **Kaplitt MG**, Abbey MV, During MJ, Leone P, Langer D, MJ O'Connor and Freese A (1997) Adenovirus vector-mediated gene transfer into human epileptogenic brain slices: prospects for gene therapy in epilepsy. *Exp Neurol* **148**:167-78.

26. Rosenfeld MR, Bergman I, Schramm L, Griffin JA, **Kaplitt MG**, Meneses PI (1997). Adeno-associated viral vector gene transfer into leptomeningeal xenografts. *J Neurooncol* **34**(2): 139-44.
27. Sugiyama A, Hattori S, Tanaka S, Isoda F, Kleopoulos S, Rosenfeld M, **Kaplitt M**, Sekihara H, Mobbs C (1997) Defective adeno-associated viral-mediated transfection of insulin gene by direct injection into liver parenchyma decreases blood glucose of diabetic mice. *Horm Metab Res* **29**:599-603.
28. During MJ, Samulski RJ, Elsworth JD, **Kaplitt MG**, Leone P, Xiao X, Li J, Freese A, Taylor JR, Roth RH, Sladek JR, O'Malley KL, Redmond DE (1998) In vivo expression of therapeutic human genes for dopamine production in the caudates of MPTP-treated monkeys using an AAV vector. *Gene Therapy* **5**:820-827.
29. **Kaplitt MG**, Darakchiev BJ, During MJ (1998) Prospects for gene therapy in pediatric neurosurgery. *Pediatr Neurosurg* **28**:3-14.
30. During MJ, Xu R, Young D, **Kaplitt MG**, Sherwin RS, Leone P (1998) Peroral gene therapy of lactose intolerance using an adeno-associated virus vector. *Nat Med* **4**:1131-1135.
31. Yin J, **Kaplitt MG**, Kwong AD, Pfaff DW (1998) In situ PCR for in vivo detection of foreign genes transferred into rat brain. *Brain Res* **783**:347-354.
32. Kanno H, Hattori S, Sato H, Murata H, Huang FH, Hayashi A, Suzuki N, Yamamoto I, Kawamoto S, Minami M, Miyatake S, Shuin T, **Kaplitt MG** (1999) Experimental gene therapy against subcutaneously implanted glioma with a herpes simplex virus-defective vector expressing interferon-gamma. *Cancer Gene Ther* **6**:147-154
33. Thomas DL, Shin S, Jiang BH, Vogel H, Ross MA, **Kaplitt M**, Shenk TE, Javier RT (1999) Early region 1 transforming functions are dispensable for mammary tumorigenesis by human adenovirus type 9. *J Virol* **73**:3071-3079
34. Bilsky MH, Downey RJ, Kaplitt MG, Elowitz EH, Rusch VW (2001) Tension pneumocephalus resulting from iatrogenic subarachnoid-pleural fistulae: report of three cases. *Ann Thorac Surg* **71**:455-457.
35. During MJ, **Kaplitt MG**, Stern MB, Eidelberg D (2001) Subthalamic GAD gene transfer in Parkinson's disease patients who are candidates for deep brain stimulation. *Hum Gene Ther* **12**:1589-1591.
36. Luo J, **Kaplitt MG**, Fitzsimons HL, Zuzga D, Raniga S, Oshinsky M, During MJ (2002) Subthalamic GAD gene therapy in a Parkinson's disease rat model. *Science* **298**:425-429.
37. Moussatov S, Roberts J, Pfaff D and **Kaplitt MG** (2002) A cis-acting element that directs exclusively circular adeno-associated virus replication and packaging. *J. Virol.* **76**:12792-12802.

38. **Betchen S and Kaplitt MG** (2003) Current and future surgical therapies for Parkinson's Disease. *Curr. Op. Neurol.* **16**:487-494.
39. Scott RE, Wu-Peng XS, **Kaplitt MG**, Pfaff DW (2003) Gene transfer and in vivo promoter analysis of the rat progesterone receptor using a herpes simplex virus viral vector. *Mol. Brain Res.* **114**:91-100.
40. Musatov S, Roberts J, Brooks AI, Pena J, Betchen S, Pfaff DW and **Kaplitt MG**. The PTEN anti-oncogene negatively regulates the neuronal phenotype in PC12 cells. *Proc. Natl. Acad. Sci. USA*, In press.
41. Betchen S, Musatov S, Roberts J and **Kaplitt MG**. PTEN inhibits adrenomedullin expression and function in brain tumor cells. Submitted, Cancer Research.
42. Fraser J, Brooks AI, Sugiultzoglul M, Roberts J, Musatov S and **Kaplitt MG**. Effects of deep brain stimulation on gene expression in the rat striatum. Submitted, Neurosurgery.
43. Becker JB, von Esenwein S, Musatov S, Toran-Allerand D, Bennett AL, **Kaplitt MG**, Insel T and Young LJ. Viral vector-induced over-expression of estrogen receptor-alpha in striatum enhances the behavioral effects of estradiol. Submitted, Journal of Neuroscience.

RESEARCH SUPPORT

Neuroscience Initiative Funding

Agency: Weill Medical College of Cornell University

Amount: \$750,000 over three years

P.I. Kaplitt

Type: Institutional Start-Up funding, 7/1/01-6/30/04

Effect of PTEN Anti-Oncogene on Age-Related Neurodegenerative Disorders

P.I.: Kaplitt

Agency: Ellison Foundation for Medical Research

Amount: \$200,000 over four years

Type: Grant, 7/1/02-6/30/06

Influence of PTEN Anti-Oncogene on Pathways Associated with Alzheimer's Disease

P.I. Kaplitt

Agency: New York Academy of Medicine

Amount: \$50,000

Type: Fellowship, 7/1/02-6/30/03

PTEN Anti-Oncogene Influences on Neuronal Function

P.I. Kaplitt

Agency: National Institute of Neurological Disorders and Stroke

Amount: \$135,000 per year

Type: KO8 Career Development Award, Pending

Influence of PTEN Anti-Oncogene on Glucose Homeostasis

P.I. Kaplitt

Agency: National Institute of Diabetes and Digestive and Kidney Diseases

Amount: \$200,000 over two years

Type: R21 Pilot Project Award, Pending